Radiation-Induced Cavernous Hemangiomas: Case Report and Literature Review

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ABSTRACT: The case of a 51-year-old man diagnosed with two acquired cavernous hemangiomas 17 years after cranial irradiation for a cerebellar astrocytoma is reported. A review of 84 cases of radiation-induced cavernous hemangiomas found in the literature is presented. In this series the mean age at the time of irradiation (±SD) was 10.4 ±2.0 years (median = 8 years), while the mean time to cavernous hemangioma diagnosis (±SD) was 10.3 ±1.9 years (median = 8 years). Time to cavernous hemangioma diagnosis was found to be inversely related to radiation dose. Hemorrhage from radiation-induced cavernous hemangiomas was found in 40.0% of patients, with an incidence of 3.9% per patient year. An inverse trend was identified between radiation dose and symptomatic presentation, cavernous hemangioma hemorrhage or surgical resection. This review of radiation-induced cavernous hemangiomas confirms that both younger patients and those who received a larger dose of radiation are at increased risk of radiation-induced cavernous hemangiomas. Our results suggest that, based on an assessment of CT or MR images, there may be an increased risk of hemorrhage when comparing radiation-induced to congenital cavernous hemangiomas. Increasing radiation doses appear to stabilize these lesions, decreasing the risk of a symptomatic presentation, cavernous hemangioma hemorrhage and surgical intervention.

RÉSUMÉ: Observation et revue de la littérature sur les hémangiomes caverneux induits par l'irradiation. Nous rapportons l'observation clinique d'un homme de 51 ans chez qui on a constaté la présence de deux hémangiomes caverneux acquis, 17 ans après une irradiation crânienne pour un astrocytome cérébelleux. Nous présentons une revue de la littérature portant sur 84 cas d'hémangiomes caverneux induits par l'irradiation. L'âge moyen (± écart type) au moment de l'irradiation était de 10,4 ± 2,0 ans (médiane de 8 ans) et le temps moyen écoulé de l'irradiation jusqu'au moment du diagnostic était de 10,3 ± 1,9 ans (médiane de 8 ans). La longueur de cette période de temps était inversement reliée à la dose de radiation. Une hémorragie dans l'hémangiome caverneux induit par l'irradiation était présente chez 40,0% des patients et son incidence était de 3,9% par patient-année. Nous avons observé une tendance inverse entre la dose de radiation et l'apparition de la symptomatologie, l'hémorragie au niveau de l'hémangiome caverneux ou la résection chirurgicale. Cette revue portant sur les hémangiomes caverneux induits par l'irradiation confirme que, tant chez les patients plus jeunes que chez ceux qui ont reçu une dose plus élevée de radiation, le risque d'hémangiomes caverneux induits par l'irradiation est plus élevé. Nos résultats d'évaluation de l'imagerie PET ou IRM sont compatibles avec la possibilité d'un risque plus élevé d'hémorragie si l'hémangiome caverneux est induit par l'irradiation que s'il est congénital. Des doses croissantes de radiations semblent stabiliser ces lésions, diminuant ainsi le risque de symptômes, d'hémorragie et de chirurgie.

Cavernous hemangiomas (cavernoma, cavernous angioma, cavernous malformation, cryptic vascular malformation) are mulberry-like assemblages of vascular sinusoids that are lined by a single endothelial layer. A lack of intervening parenchyma distinguishes these lesions from other types of vascular malformations. They contain blood products at various stages of thrombosis and degradation and are often surrounded by varied quantities of hemosiderin, gliosis and calcification. They may be found in any location in the central nervous system, including the spinal cord and ventricles.[1] Cavernous hemangiomas have been found to be as prevalent as 0.6% in some large prospective cohorts.[2]

These malformations were initially thought to be congenital, with some known instances of familial cases.[3] In 1990, Wilson hypothesized that cavernous hemangiomas could be acquired following cranial irradiation.[4] In 1994, Circillo et al presented seven such cases.[5] A further 82 cases have since been described.[6-34] However, in spite of the increasing number of

reported cases the mechanism(s) of their formation is poorly understood.

This report describes the case of a man irradiated for the treatment of a cerebellar astrocytoma who, 17 years after treatment, demonstrated radiographic evidence of two distinct cavernous hemangiomas illustrating the long-term evolution of this disorder. Previous authors have suggested a relationship between radiation-induced cavernous hemangiomas to patient age and radiation dose.[15,18,20,31] An increased incidence of hemorrhage in radiation-induced as compared to familial or sporadic cavernous hemangiomas has been commented on.[14,20,28,31,35,36] However, these reports have included small numbers of patients which makes their results difficult to generalize to all patients with radiation-induced cavernous hemangiomas.

This report reviews the cases of radiation-induced cavernous hemangiomas reported in the literature. Using methods of statistical analysis, factors influencing: 1) the time interval between irradiation and the initial diagnosis of the cavernous hemangioma(s); 2) the number of identified acquired cavernous hemangiomas; 3) the presence of associated symptoms, cavernous hemangioma hemorrhage and the prevalence of surgical intervention have been assessed. The hypothesis that radiation induces cavernous hemangiomas via a two-hit mechanism, occurring in a variety of different radiation induced genetic micro-environments, involving both endothelial and other periluminal cells, is discussed.

CASE REPORT

A 14-year-old, right handed, boy presented to the Montreal Neurological Hospital in April, 1970 with sudden occipital headache and emesis followed by rapidly progressing somnolence. Angiography revealed a space-occupying lesion in the left cerebellar hemisphere. The patient underwent subtotal resection of a tumour, due to extension into the brainstem, and the neuropathological diagnosis was consistent with a Grade I cerebellar astrocytoma. As a result of the subtotal resection, the patient subsequently received a dose of 58 Gy to the residual tumour through opposing fields.

Follow-up CT scans performed in 1979 and 1984 revealed no evidence of any tumour progression. In 1987, 17 years after the initial irradiation, the patient complained of increasing difficulty walking as well as associated episodes of dizziness. Magnetic resonance imaging revealed a recurrent left hemispheric multi-cystic cerebellar tumour. A subtotal resection was performed in May, 1987 and neuropathology confirmed the presence of a recurrent Grade 1 cerebellar astrocytoma. The MRI also revealed two new, well-defined areas of increased signal intensity surrounded by regions of signal void in the right temporal and right parietal lobes (Figure 1). These were felt to be radiographically consistent with the diagnosis of cavernous hemangiomas. In 1988 the patient reported episodes of transient left temporal field blurring. In 1989 he began to have episodes of transient left hemianopsia associated with disturbances in left arm movement and sensation lasting five to ten minutes. In 2002,

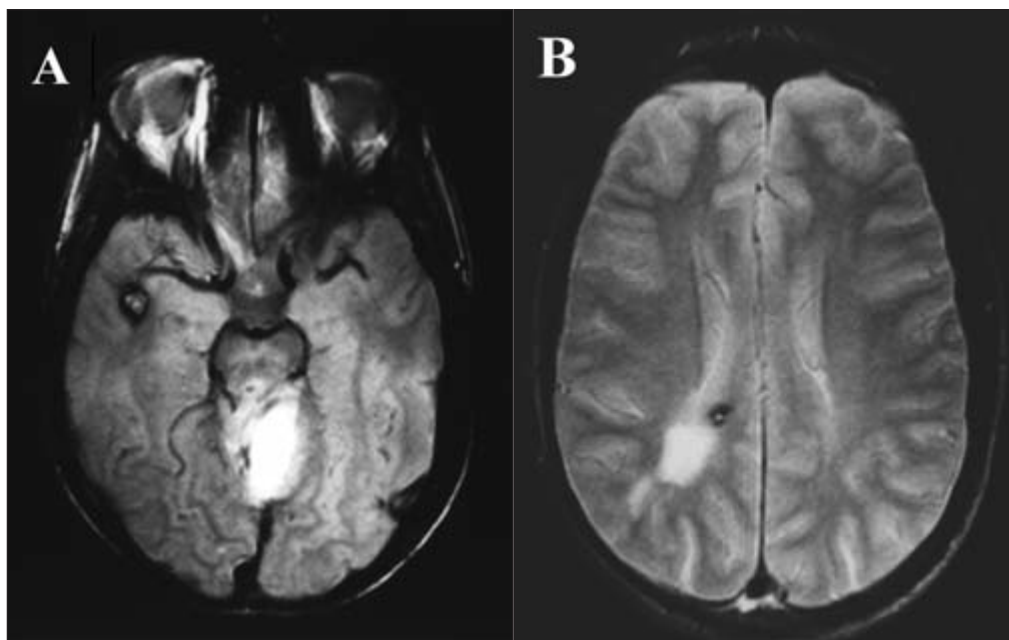*Figure 1:* A 51-year-old man who, at the age of 14, was treated with 58 Gy of radiation for a Grade 1 cerebellar astrocytoma. Seventeen years later, MR revealed the region of recurrent tumour and two previously undiagnosed hyperintense lesions surrounded by regions of signal void in the right temporal lobe (Figure A) and right parietal lobe (Figure B). The diagnosis of radiation-induced cavernous hemangiomas was made.

32 years after his initial presentation, he suffered two generalized seizures. Since that time his seizures have been well controlled on anti-convulsant therapy. No hemorrhage or other changes in the cavernous hemangiomas have been identified since the lesions were initially diagnosed.

LITERATURE ANALYSIS: PATIENTS AND METHODS

MEDLINE and EMBASE were searched (1966 to March 2006) using two keywords: cavernous hemangioma and radiation-induced neoplasms. Additional cases were included from the bibliographic references of the identified articles. Cases were included whether the cavernous hemangioma(s) were identified by histological examination or radiographic imaging.

The data collected from each case included: patient sex, age at irradiation, total radiation dose, presenting cavernous hemangioma symptoms, latency to cavernous hemangioma(s) diagnosis, number of cavernous hemangiomas identified, as well as the presence of hemorrhage on neuro-imaging and surgical intervention. When evaluating irradiation dose, the irradiation dose delivered to the area which subsequently gave rise to the cavernous hemangioma(s) was considered. Our assumption was that radiation-induced lesions require direct exposure to radiation in order to develop. Due to incomplete data present in the literature no distinction could be made between symptomatic and asymptomatic hemorrhagic events.

The Spearman rank correlation was used to explore the relationship between radiation dose and latency to diagnosis, as well as the age at irradiation and the latency to diagnosis. Statistical significance was defined as a *p* value <0.05.

The two-sided Wilcoxon rank-sum test was used to evaluate the relationship between latency to diagnosis, cavernous hemangiomas hemorrhage and the presence of multiple cavernous hemangiomas. The relationship between age at irradiation and hemorrhage or multiple cavernous hemangiomas was examined. The relationship between radiation dose and symptomatic presentation, cavernous hemangioma hemorrhage, surgical intervention or the presence of multiple cavernous hemangiomas were also assessed. Statistical significance was defined as a *p* value <0.05.

LITERATURE ANALYSIS: RESULTS

Eighty-nine cases of radiation-induced cavernous hemangiomas were identified in the literature. Of these, five were excluded because they were not clearly identified and/or characterized by the authors.[15] Thus, 85 cases were included in the analysis (84 derived from the literature, one from the current report) the details of which are described in Table 1. The demographics of these cases are summarized in Table 2. Two or more cavernous hemangiomas were found in 41% of patients. Forty percent of patients had evidence of hemorrhage on their investigations resulting in an estimated incidence of 3.9% per patient year [(34 events of hemorrhage)/(874 patient years of latency)]. Thirty-nine percent of patients underwent surgical intervention, predominately for the management of symptomatic cavernous hemangioma hemorrhage.

Age at Irradiation and Time to Diagnosis

Figure 2 illustrates the age distribution of the cases reviewed at the time of irradiation and the latency in years to cavernous hemangioma(s) diagnosis. Mean age at the time of radiation (±SD) was 10.4 ±2.0 years (median eight years) while the mean time latency to diagnosis (±SD) was 10.3 ±1.9 years (median eight years). Table 3 outlines the presenting symptoms of the 85 cases. Fifty-eight percent of patients were asymptomatic at the

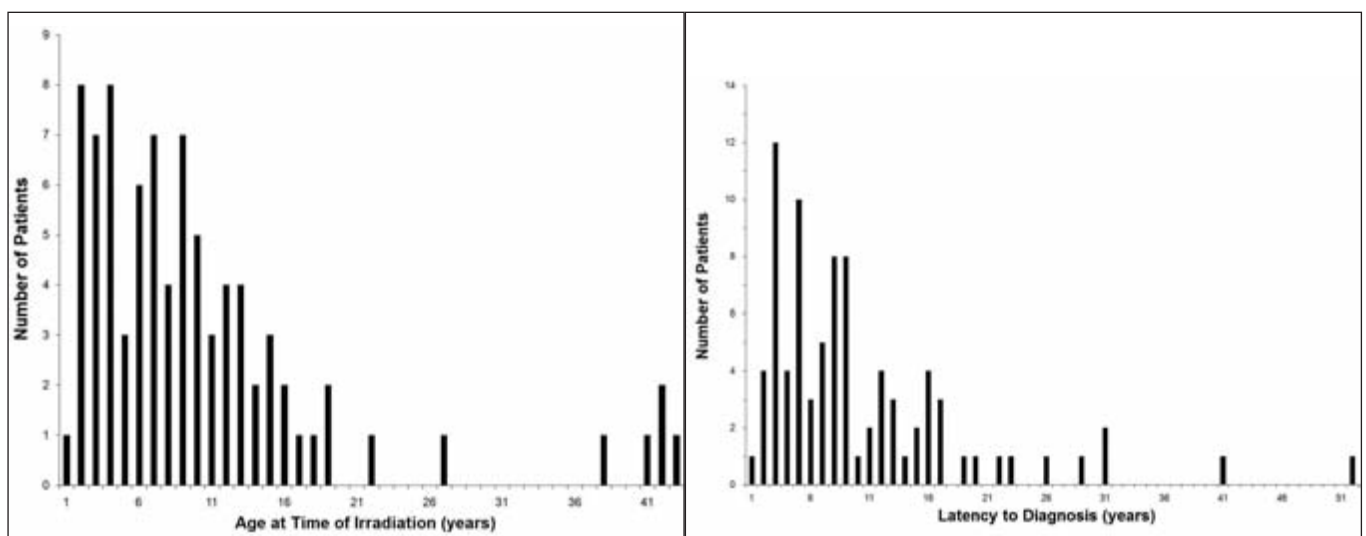

Figure 2: *Distribution of age at time of radiation (mean ±SD = 10.4 ±2.0 years, median = 8 years) and time latency to diagnosis (mean ±SD = 10.3 ±1.9 years, median = 8 years) of 85 cases of radiation-induced cavernous hemangiomas.*

Table 1: Reported cases of radiation-induced cavernous hemangiomas

Patient number	Study	Sex	Original tumour	Age at irradiation (years)	Time interval to diagnosis (years)	Radiation dose (Gy)	Hemorrhage	Surgery	>1 cavernoma
1	Amirjamshidi et al. 2000	F	cerebellar ependymoma	7	9	54	N†	Y‡	Y
2	Alexander et al. 1998	M	chromophobic adenoma	22	31	30.5	N	N	N
3	Baumgartner et al. 2003	*	medulloblastoma	5	9	55	N	Y	Y
4		*	ependymoma	2	14	45	Y	Y	Y
5		*	midbrain astrocytoma	2	19	51	Y	Y	Y
6	Bejjani et al. 1997	F	cerebellar astrocytoma	3	52	*	Y	Y	N
7	Bentele et al. 2000	M	medulloblastoma	9	3	55	Y	N	N
8	Brassard et al. 1999	M	pilocytic astrocytoma	18	5	42	N	Y	N
9	Calenbergh et al. 2003	F	pilocytic astrocytoma	7	12	56	Y	Y	N
10	Chang et al. 1998	F	choroid plexus papilloma	4	9	36	N	Y	Y
11	Circillo et al. 1994	M	medulloblastoma	3	3	55	Y	N	N
12		M	medulloblastoma	5	2	72	N	N	N
13		F	astrocytoma	8	5	45	N	N	N
14		M	astrocytoma	2	9	45	N	N	N
15		M	medulloblastoma	12	8	55	N	N	N
16		M	ALL§	5	16	24	N	N	Y
17		M	astrocytoma	6	2	50	N	N	Y
18	Duhem et al. 2005	M	leukemia	4	18	25	N	N	N
19		M	medulloblastoma	9	4	55	Y	Y	Y
20		M	pineal germinoma	10	6	50	Y	N	N
21		M	cerebellar ganglioglioma	11	16	50	N	N	N
22		M	medulloblastoma	12	16	50	Y	N	N
23		M	ependymoma	13	7	55	N	N	N
24		F	leukemia	10	5	50	Y	Y	Y
25		F	ependymoma	7	5	55	Y	Y	Y
26		F	medulloblastoma	6	22	25	N	N	Y
27	Findlay et al. 1994	F	ALL	3	20	24	N	N	N
28	Furuse et al. 2005	M	astrocytoma	27	53	60	N	Y	N
29		M	astrocytoma	42	53	60	Y	Y	Y
30	Humpl et al. 1997	M	ALL	16	2	24	Y	Y	N
31		F	ALL	3	8	18	Y	Y	Y
32		M	ALL	9	11	18	Y	Y	N
33		M	ALL	2	12	18	Y	N	N
34	Jabbour et al. 2004	M	Wilm's tumour	4	29	?	N	Y	Y
35	Jain et al. 2005	F	medulloblastoma	3	18	54	N	N	Y
36		M	ependymoma	3	6	50.4	Y	Y	Y
37		M	medulloblastoma	3	34	36	N	N	N
38		M	germinoma	13	21	50.4	Y	N	N
39		F	cushing's disease	16	57	*	N	N	N
40	Laitt et al. 1995	F	ALL	6	18	24	Y	N	N
41	Larson et al. 1998	M	ALL	6	7	18	Y	Y	Y
42		M	ALL	2	12	24	N	N	N
43		M	ALL	7	12	18	Y	Y	N
44		F	medulloblastoma	9	3	90	N	N	N
45		F	astrocytoma	7	3	54	Y	Y	N
46		M	glioma	15	4	54	N	N	N
47	Lew et al. 2006	M	medulloblastoma	4	13	54	N	N	N
48		F	medulloblastoma	8	13	72	N	N	Y
49		M	medulloblastoma	9	8	72	N	N	N
50		F	medulloblastoma	6	8	72	N	N	N
51		M	medulloblastoma	19	16	54	N	N	Y
52		M	medulloblastoma	4	6	72	N	N	N
53		F	medulloblastoma	1	10	54	N	N	Y
54		F	medulloblastoma	4	3	56	N	N	N
55		F	medulloblastoma	9	9	72	N	N	N
56		F	medulloblastoma	11	5	54	N	N	N
57		M	medulloblastoma	2	5	51	N	N	Y
58		M	medulloblastoma	9	2	56	Y	N	N
59		F	medulloblastoma	11	3	72	N	N	N
60		M	medulloblastoma	6	5	56	Y	Y	Y
61		M	medulloblastoma	2	8	54	N	N	Y
62		M	medulloblastoma	10	3	56	N	N	Y
63		F	medulloblastoma	7	1	56	N	N	Y
64		F	medulloblastoma	13	4	71	N	N	N
65	Maeder et al. 1998	M	medulloblastoma	14	3	36	N	N	Y
66	Maraire et al. 1999	M	germinoma	17	5	27	Y	Y	N
67	Megdiche Bazarcacha et al. 2004	F	pilocytic astrocytoma	12	3	56	N	N	N
68	Miyamoto et al. 1994	F	anaplastic meningioma	41	7	50	Y	N	Y
69	Narayan et al. 1998	M	medulloblastoma	4	13	27	N	Y	N
70	Noël et al. 2002	F	oligodendroglioma	38	7	60	Y	N	Y
71		F	lymphoma	7	3	24	Y	N	N
72		F	cavernous angioma	19	8	30	N	N	Y
73		M	medulloblastoma	4	15	*	N	N	Y
74	Novelli et al. 1997	M	medulloblastoma	13	23	36.91	N	N	Y
75		M	ependymoma	2	9	*	N	N	N
76	Olivero et al. 2000	M	lung carcinoma brain metastasis	42	5	55	Y	Y	N
77	Pozzati et al. 1996	F	astrocytoma	10	6	30	Y	Y	N
78		F	pituitary adenoma	43	9	50.5	N	Y	N
79		F	dysgerminoma	15	7	50	Y	Y	N
80		F	cavernous angioma	15	9	75	Y	Y	Y
81		M	astrocytoma	12	3	54	Y	N	N
82	Sugiyama et al. 2002	F	neuroectodermal tumour	10	4	55	Y	N	N
83		M	pineal mixed germ cell	8	5	60	N	N	N
84	Yoshino et al. 2005	F	spinal pilocytic astrocytoma	8	8	60	N	Y	Y

* = data not reported; † = absent; ‡ = present; § = acute lymphoblastic leukemia

time of diagnosis and usually identified on routine follow-up investigations. The remaining 48% presented with various combinations of seizure, headache, emesis, and motor dysfunction.

Time Latency to Cavernous Hemangiomas Diagnosis

There was a significant decrease in latency to diagnosis with increasing radiation dose, as demonstrated in Figure 3 (R^2=0.10, p=0.015). Conversely, age at the time of tumour irradiation did not have a significant relationship with latency to diagnosis, as shown in Figure 4 (R^2<0.003, p=0.124).

Symptomatology, Hemorrhage and Surgical Intervention

A significant inverse trend appeared to exist between radiation dose and the presence of symptoms, cavernous hemangiomas hemorrhage or surgical intervention. Among those patients who presented without significant symptoms, the mean radiation dose (±SD) received by each patient was 53.4 ±14.4 Gy as opposed to 42.2 ±16.3 Gy among patients who were symptomatic (p=0.011). Those with no reported cavernous hemangioma hemorrhage received a mean radiation dose (±SD) of 51.6 ±15.7 Gy as opposed to those found to have cavernous hemangioma hemorrhage who had a mean radiation dose (±SD) of 44.0 ±16.0 Gy (p=0.062). Finally, among those patients who did not undergo surgery, the mean radiation dose (±SD) was 51.4 ±15.9 Gy as compared to 43.9 ±15.7 Gy among those did undergo surgical treatment (p=0.065).

Multiple Cavernomas

There was no significant relationship between the development of multiple cavernous hemangiomas and radiation dose, age at irradiation, or latency to diagnosis (p=0.702, p=0.103, p=0.42).

Discussion

Cavernous hemangiomas are a well-recognized vascular malformation. Current research suggests that radiation-induced cavernous hemangiomas are common sequelae of radiotherapy. In a recent series, Lew et al demonstrated a cumulative incidences of 5.6, 14 and 43% at three, five and ten years after irradiation in pediatric medulloblastoma patients.[21] These results highlight the importance of gaining a better understanding of this disorder.

Age at Irradiation

Previous authors have proposed that children demonstrate a greater susceptibility to the development of radiation-induced cavernous hemangiomas.[15,18,20,27,31] Our review confirms these findings. The average age at irradiation was 10.4 years (median age eight years). Of the 85 cases reviewed, only seven were patients irradiated at ≥20 years of age (8.2%), while 56 were irradiated at ≤10 years of age (65.9%). The reason that the immature brain rather than the adult brain responds to radiation by the more frequent formation of cavernous hemangiomas over extended periods of time is unknown. This could be related to a differential response of the immature brain to radiation injury in a background of vastly different gene expression profiles.[37] It has

Table 2: The characteristics of the 85 cases of cavernous hemangiomas reviewed

Characteristic	Value
Sex	57.0% male
>1 Cavernous Hemangioma	41.2%
Cavernous hemangioma hemorrhage	40.0%
Surgical intervention	38.8%
Radiation dose	Mean ±SD = 48.5 ±3.5 Gy
	Median = 54
Age at irradiation	Mean ±SD = 10.4 ±2.0 yrs
	Median = 8
Age at cavernoma diagnosis	Mean ±SD = 20.6 ±2.7 yrs
	Median = 17
Latency to diagnosis	Mean ±SD = 10.3 ±1.9 yrs
	Median = 8

yrs=years

Figure 3: Eighty cases demonstrating an inverse correlation between total radiation dose and latency to cavernous hemangiomas diagnosis.

also been suggested that patients irradiated at younger ages develop cavernous hemangiomas at a faster rate (i.e. with a faster latency).[15,35] Our study does not support this concept since it demonstrates that the age at irradiation bears no direct relationship to the latency to diagnosis. The fact that some pediatric CNS tumours tend to follow a more benign course may explain why the majority of radiation-induced cavernous hemangiomas occur in the young where the prognosis is sufficiently extended to allow for the consequences of radiation therapy to be fully realized.

Radiation Dose

Previous authors have demonstrated an inverse relationship between radiation dose and latency to diagnosis and our results are consistent with this finding.[15] The proposed mechanisms include more extensive damage to nervous tissue with increasing radiation doses, hence the more rapid development of vascular malformations such as cavernous hemangiomas. However, increased radiation doses are associated with patients who are less likely to present with symptoms, to demonstrate evidence of cavernous hemangioma hemorrhage or require surgical intervention. This would suggest that patients who receive increased doses of radiation develop cavernous hemangiomas more quickly, but the cavernous hemangiomas that these patients do develop are less likely to have a significant impact on their clinical condition.

It has been suggested that low radiation doses are more efficient at inducing cavernous hemangiomas. The literature supporting this concept includes the observation that cavernous hemangiomas usually arise at the fringe of the main radiation field as opposed to the center, as seen in this case report.[35] This potentially reflects the fact that the radiation delivered at the center of the field may result in extensive cellular apoptosis thus preventing subsequent cave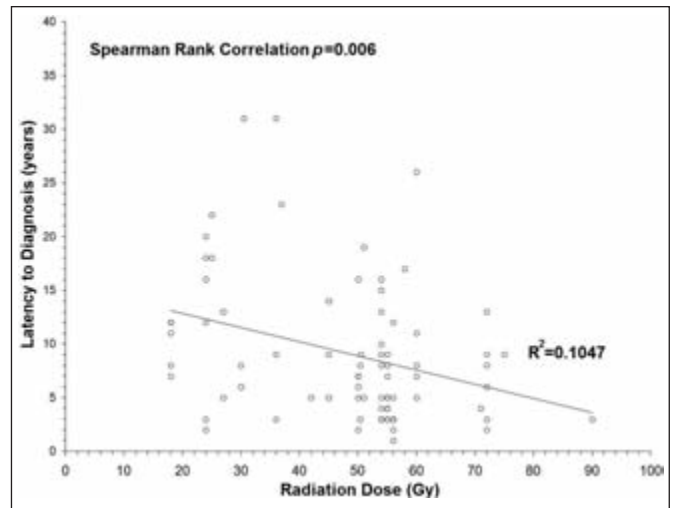rnous hemangiomas formation. The periphery of the field is subject to radiation doses that alter genetic stability without substantial cell apoptosis.

Hemorrhage

Interest in radiation-induced cavernomas is related to the possibility that they represent a significantly greater risk of spontaneous hemorrhage than sporadic cavernous hemangiomas.[14,20,28,31,35,36] The reported rate of hemorrhage among sporadic cases of cavernous hemangiomas has ranged from 0.25% to 3.1% per patient year.[38-42] This review has found that 40.0% of reported radiation-induced cavernous hemangiomas demonstrated evidence of hemorrhage on CT or MRI resulting in an incidence of 3.9% per patient year. Because

Table 3: Presenting symptoms of the 85 cases of cavernous hemangiomas reviewed

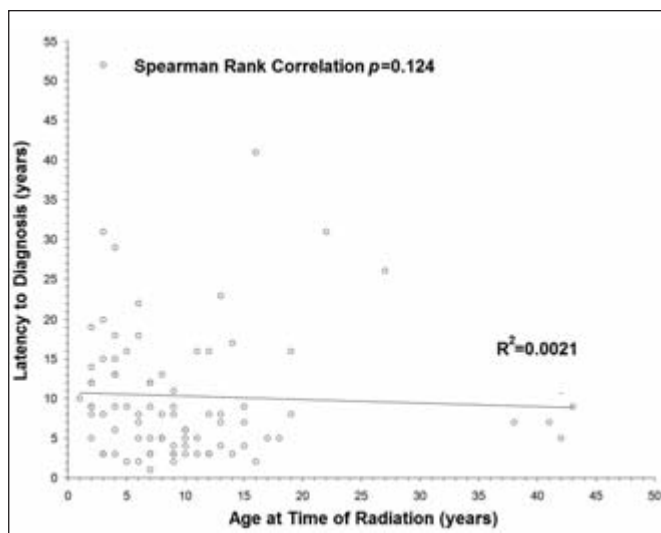| Symptom	Prevalence
Asymptomatic	49 (57.6%)
Seizure	14 (16.4%)
Headache	8 (9.4%)
Motor dysfunction	6 (7.1%)
Emesis	5 (5.9%)
Symptomatic hemorrhage	4 (4.7%)
Bulbar signs & symptoms	4 (4.7%)
Sensory dysfunction	3 (3.5%)
Syncope	2 (2.4%)
Back pain/stiffness	1 (1.2%)

Figure 4: Eighty-five cases demonstrating no significant correlation between age at irradiation and time latency to diagnosis of the cavernous hemangiomas.

of an incomplete data set we were unable to quantify asymptomatic and symptomatic hemorrhages in this study. However the incidence of asymptomatic and symptomatic hemorrhage identified suggests that radiation-induced cavernous hemangiomas may be at greater risk of hemorrhage than congenital cavernous hemangiomas. In fact, our estimate of 3.9% per patient year is an under-estimation considering that these radiation-induced cavernomas almost certainly did not develop immediately following patient irradiation. Therefore during only a portion of those 874 years of latency (see results) was there a cavernoma to undergo hemorrhage.

A publication bias may exist where those patients with symptomatic hemorrhage are more likely to be reported in the literature. However, we believe that this bias would be small considering that post-radiation patients generally receive very thorough medical follow-up including repeat neuro-imaging.

Lew et al, in a large case series, suggested that the overwhelming majority of radiation-induced cavernous hemangiomas do not result in symptomatic hemorrhage and do not require surgical intervention.[21] However, in addition to a small sample limited to medulloblastoma patients less than 21 years of age, the mean follow-up time in that case series was 7.2 years. This review demonstrates a mean latency to cavernous hemangiomas diagnosis of 10.3 years, implying that the follow-up period in Lew et al report may have been too short.

The very definition of hemorrhage remains controversial. Some authors have proposed radiological definitions while others have suggested that neurological deterioration should be used as an indicator of cavernous hemangioma hemorrhage, irrespective of radiographic evidence of hemorrhage.[40] Although we acknowledge this controversy, we believe that radiological evidence of hemorrhage remains the most accepted means of

detecting hemorrhage, the method used by all of the studies cited in this review.

Multiple Cavernous Hemangiomas

Results reported by Baumgartner et al supported the possibility that patients irradiated at younger ages are more likely to develop multiple cavernomas.[9] Duhem et al suggested that certain patients develop multiple cavernomas due to genetic predispositions.[35] This review demonstrates that multiple cavernous hemangiomas occur independently of age at irradiation, latency to diagnosis or radiation dose. These findings suggest that individual patient factors including genetic predisposition to radiation may be critical in the development of multiple cavernous hemangiomas.

Pozzatti et al have described two cases of cavernous hemangiomas with associated venous malformations.[31] A possible association between these two vascular malformations and radiation has been previously reported.[31] Unfortunately, the information present in the studies we reviewed does not allow us to make a comment on the frequency in which venous malformations are seen after radiation injury with or without the presence of cavernous hemangiomas.

Etiology

The data in the literature is most consistent with a two-hit hypothesis in the pathogenesis of radiation-induced cavernous hemangiomas. In mouse models, cavernous hemangioma have been shown to develop only after a gene mutation in CCM1/KRIT-1, one of the genes responsible for hereditary cavernous hemangiomas which is involved in endothelial cell-cell junction integrity, is associated with a second cellular mutation in p53, a tumour-suppressor gene involved in apoptosis.[43]

One possible model for radiation-induced cavernous hemangioma development would be that at the time of irradiation, some periluminal cells have a pre-existing mutation/alteration in the p53 gene resulting in a genetic susceptibility to cavernous hemangioma formation. The irradiation then facilitates the development of this malformation by inducing a mutation in CCM1/KRIT-1 or another of the known (CCM2/MGC4607 and CCM3/PDCD10 genes) or unknown genes responsible for hereditary cavernous hemangioma development. Mutations in p53 are common in CNS neoplasms, with a prevalence ranging from 1% in medulloblastomas to 42% in low-grade astrocytomas.[44] The higher rate of p53 mutations in low-grade astrocytomas may partially explain why cavernous hemangiomas have been found with a variety of low grade tumours. Cavernous hemangiomas have also been reported associated with low grade astrocytomas, oligodendrogliomas, schwannomas and a rare lesion called angioglioma.[45-48]

A pre-existing genetic predisposition with a mutation or epigenetic alteration in CCM1, CCM2 or CCM3 gene(s) associated with a radiation-induced p53 mutation may also result in a genetic environment necessary for the development of cavernous hemangiomas. The possibility that both of these events could be induced by irradiation alone is unknown.

Another possible model of radiation-induced cavernous hemangioma pathogenesis may involve a germ line mutation in

CCM1 (or CCM2 and CCM3) that is associated with a radiation-induced somatic line mutation in one of these three genes. Gault et al demonstrated evidence in humans supporting a two-hit hypothesis where a cavernous hemangioma possessed both a germ as well as a somatic line CCM1 mutation.[49]

The hypothesis that radiation induced cavernous hemangiomas occur in a variety of different radiation induced genetic micro-environments involving both endothelial and other periluminal cells appears to be most consistent with the present knowledge base. The possibility that immunological mechanisms may be involved in the continuing growth of these lesions has been proposed.[50]

CONCLUSION

Cavernous hemangiomas are important sequelae of radio-therapy, particularly in the pediatric population. An understanding of the development and unique characteristics of radiation-induced cavernous hemangiomas is important for clinicians delivering radiotherapy, involved in subsequent patient medical follow-up and managing any discovered acquired cavernous hemangiomas. Further investigations, in the form of prospective clinical trials, are required to conclusively identify and characterize those patients who are at risk, the natural history of these acquired lesions and the most appropriate management.

ACKNOWLEDGMENTS

REFERENCES

1. Raychaudhuri R, Batjer HH, Awad IA. Intracranial cavernous angioma: a practical review of clinical and biological aspects. Surg Neurol. 2005;63(4):319-28.
2. Kim DS, Park YG, Choi JU, Chung SS, Lee KC. An analysis of the natural history of cavernous malformations. Surg Neurol. 1997; 48(1):9-18.
3. Labauge P, Denier C, Bergametti F, Tournier-Lasserve E. Genetics of cavernous angiomas. Lancet Neurol. 2007;6(3):237-44.
4. Wilson CB. Cryptic vascular malformations. Clin Neurosurg. 1992; 38:49-84.
5. Circillo SF, Cogen PH, Edwards MS. Pediatric cryptic vascular malformations: presentation, diagnosis and treatment. Pediatr Neurosurg. 1994;20(2):137-47.
6. Chang SD, Vanefsky MA, Havton LA, Silverberg GD. Bilateral cavernous malformations resulting from cranial irradiation of a choroid plexus papilloma. Neurol Res. 1998;20(6):529-32.
7. Alexander MJ, DeSalles AA, Tomiyasu U. Multiple radiation-induced intracranial lesions after treatment for pituitary adenoma. Case report. J Neurosurg. 1998;88(1):111-5.
8. Amirjamshidi A, Abbassioun K. Radiation-induced tumours of the central nervous system occurring in childhood and adolescence. Four unusual lesions in three patients and a review of the literature. Childs Nerv Syst. 2000;16(7):390-7.
9. Baumgartner JE, Ater JL, Ha CS, Kuttesch JF, Leeds NE, Fuller GN, et al. Pathologically proven cavernous angiomas of the brain following radiation therapy for pediatric brain tumours. Pediatr Neurosurg. 2003;39(4):201-7.
10. Bejjani GK, Caputy AJ, Kurtzke RN, Duong DH, Sekhar LN. Remote hemorrhage of a pontine cavernous angioma fifty-two years after cerebral irradiation. Acta Neurochir (Wien). 1997;139 (6):583-4.
11. Bentele KHP, Thobaben M, Hornung D, Kabisch H, Zeumer H. Supratentorial cavernous malformation subsequent to radical resection of an infratentorial medulloblastoma and craniospinal irradiation: was it induced by irradiation therapy? Neuropediatrics. 2000;31:A26.
12. Brassard MA, Bahary JP, Leblanc R, Bourgouin P, Berthelet F, Villemure JG. Cavernous hemangioma after stereotactic radiotherapy. J Radiosurg. 1999;2(3):195-8.
13. Campeau NG, Lane JI. De novo development of a lesion with the appearance of a cavernous malformation adjacent to an existing developmental venous anomaly. AJNR Am J Neuroradiol. 2005; 26(1):156-9.
14. Van Calenbergh F, Demaerel P, Sciot R, van Loon J. Acquired cerebellar cavernous angioma following childhood radiotherapy in a patient with neurofibromatosis type 1. Acta Neurol Belg. 2003;103(2):103-6.
15. Heckl S, Aschoff A, Kunze S. Radiation-induced cavernous hemangiomas of the brain: a late effect predominantly in children. Cancer. 2002;94(12):3285-91.
16. Humpl T, Bruhl K, Bohl J, Schwarz M, Stoeter P, Gutjahr P. Cerebral haemorrhage in long-term survivors of childhood acute lymphoblastic leukaemia. Eur J Pediatr. 1997;156(5):367-70.
17. Jabbour P, Gault J, Murk SE, Awad IA. Multiple spinal cavernous malformations with atypical phenotype after prior irradiation: case report. Neurosurgery. 2004;55(6):1431.
18. Jain R, Robertson PL, Gandhi D, Gujar SK, Muraszko KM, Gebarski S. Radiation-induced cavernomas of the brain. AJNR Am J Neuroradiol. 2005;26(5):1158-62.
19. Laitt RD, Chambers EJ, Goddard PR, Wakeley CJ, Duncan AW, Foreman NK. Magnetic resonance imaging and magnetic resonance angiography in long term survivors of acute lymphoblastic leukemia treated with cranial irradiation. Cancer. 1995;76(10):1846-52.
20. Larson JJ, Ball WS, Bove KE, Crone KR, Tew JM, Jr. Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children.[see comment]. J Neurosurg. 1998;88(1):51-6.
21. Lew SM, Morgan JN, Psaty E, Lefton DR, Allen JC, Abbott R. Cumulative incidence of radiation-induced cavernomas in long-term survivors of medulloblastoma. J Neurosurg. 2006;104(2 Suppl):103-7.
22. Maeder P, Gudinchet F, Meuli R, de Tribolet N. Development of a cavernous malformation of the brain. AJNR Am J Neuroradiol. 1998;19(6):1141-3.
23. Maraire JN, Abdulrauf SI, Berger S, Knisely J, Awad IA. De novo development of a cavernous malformation of the spinal cord following spinal axis radiation. Case report. J Neurosurg. 1999; 90(2 Suppl):234-8.
24. Megdiche Bazarbacha H, Nagi S, Douira Khomsi W, Sebai R, Belghith L, Touibi S. Le cavernome cerebral radio-induit. A propos d'un cas. Tunis Med. 2004;82(12):1124-7.
25. Miyamoto T, Irie F, Ukita T, Miyake H, Kuroiwa T, Nagasawa S, et al. Multiple cavernous angiomas accompanied with a convexity meningioma: a case report. No Shinkei Geka. 1994;22(11): 1053-6.
26. Narayan P, Barrow DL. Intramedullary spinal cavernous malformation following spinal irradiation. Case report and review of the literature. J Neurosurg. 2003;98(1 Suppl):68-72.
27. Nimjee SM, Powers CJ, Bulsara KR. Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. Neurosurg Focus. 2006; 21(1):e4.
28. Noel L, Christmann D, Jacques C, Kehrli P, Grebici-Guessom M, Esposito P, et al. Les angiomes caverneux cerebraux induits par la radiotherapie. J Neuroradiol. 2002;29(1):49-56.
29. Novelli PM, Reigel DH, Langham Gleason P, Yunis E. Multiple cavernous angiomas after high-dose whole-brain radiation therapy. Pediatr Neurosurg. 1997;26(6):322-5.

30. Olivero WC, Deshmukh P, Gujrati M. Radiation-induced cavernous angioma mimicking metastatic disease. Br J Neurosurg. 2000;14 (6):575-8.

31. Pozzati E, Giangaspero F, Marliani F, Acciarri N. Occult cerebrovascular malformations after irradiation. Neurosurgery. 1996;39(4):677-82.

32. Sugiyama T, Matsutani M, Ogura H, Yoshizawa H, Nishikawa R. Radiation-induced intracerebral cavernous angiomas in children with malignant brain tumours: a report of two cases. Jpn J Neurosurg. 2002;11:425-30.

33. Yoshino M, Morita A, Shibahara J, Kirino T. Radiation-induced spinal cord cavernous malformation. Case report. J Neurosurg. 2005;102(1 Suppl):101-4.

34. Findlay JM, Akabutu J, Johnson ES, McDonald S. Radiation-induced meningioma.[comment]. J Neurosurg. 1994;80(3): 594-5.

35. Duhem R, Vinchon M, Leblond P, Soto-Ares G, Dhellemmes P. Cavernous malformations after cerebral irradiation during childhood: report of nine cases. Childs Nerv Syst. 2005;21 (10):922-5.

36. Furuse M, Miyatake SI, Kuroiwa T. Cavernous malformation after radiation therapy for astrocytoma in adult patients: report of 2 cases. Acta Neurochir (Wien). 2005;147(10):1097-101.

37. Galvin JE, Ginsberg SD. Expression profiling in the aging brain: a perspective. Ageing Res Rev. 2005;4(4):529-47.

38. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. J Neurosurg. 1991; 75(5):702-8.

39. Moriarity JL, Clatterbuck RE, Rigamonti D. The natural history of cavernous malformations. Neurosurg Clin N Am. 1999;10(3): 411-7.

40. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg. 1997;87(2):190-7.

41. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. J Neurosurg. 1991;75(5):709-14.

42. Sigal R, Krief O, Houtteville JP, Halimi P, Doyon D, Pariente D. Occult cerebrovascular malformations: follow-up with MR imaging. Radiology. 1990;176(3):815-9.

43. Plummer NW, Gallione CJ, Srinivasan S, Zawistowski JS, Louis DN, Marchuk DA. Loss of p53 sensitizes mice with a mutation in Ccm1 (KRIT1) to development of cerebral vascular malformations. Am J Pathol. 2004;165(5):1509-18.

44. Hernandez-Boussard T, Rodriguez-Tome P, Montesano R, Hainaut P. IARC p53 mutation database: a relational database to compile and analyze p53 mutations in human tumours and cell lines. International Agency for Research on Cancer. Hum Mutat. 1999; 14(1):1-8.

45. Acciarri N, Padovani R, Giulioni M, Roncaroli F. Cerebral astrocytoma and cavernous angioma: a case report. Br J Neurosurg. 1994;8(5):607-10.

46. Feiz-Erfan I, Zabramski JM, Herrmann LL, Coons SW. Cavernous malformation within a schwannoma: review of the literature and hypothesis of a common genetic etiology. Acta Neurochir (Wien). 2006;148(6):647-52.

47. Palma L, Mastronardi L, Celli P, d'Addetta R. Cavernous angioma associated with oligo-astrocytoma-like proliferation. Report of two cases and review of the literature with a reappraisal of the term "angioglioma". Acta Neurochir (Wien). 1995;133(3-4): 169-73.

48. Tews DS, Bohl JE, Van Lindert E, Ringel K. Association of oligodendroglioma-like cell proliferation and angiomatous vasculature--coincidence or pathogenetically related lesions? Clin Neuropathol. 1998;17(2):69-72.

49. Gault J, Shenkar R, Recksiek P, Awad IA. Biallelic somatic and germ line CCM1 truncating mutations in a cerebral cavernous malformation lesion. Stroke. 2005;36(4):872-4.

50. Shenkar R, Shi C, Check IJ, Lipton HL, Awad IA. Concepts and hypotheses: inflammatory hypothesis in the pathogenesis of cerebral cavernous malformations. Neurosurgery. 2007;61(4): 693-703.